Trial Description

Title

Simvastatin add-on to Escitalopram in Patients With Comorbid Obesity and Major Depression: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial

Trial Acronym

SIMCODE

URL of the trial

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Brief Summary in Lay Language

Major depressive disorder (MDD) and obesity are major contributors to impaired health worldwide. Statins are among the most prescribed medications with well-established safety and efficacy. Statins are recommended in primary prevention of cardiovascular disease, which has been linked to both MDD and obesity. Moreover, statins are promising candidates to treat MDD because a meta-analysis of pilot randomized controlled trials has found antidepressive effects of statins as adjunct therapy to antidepressants. However, no study so far has tested the antidepressive potential of statins in patients with MDD and comorbid obesity. Therefore, we hypothesize that Simvastatin add-on to standard antidepressant Escitalopram will improve depression to a greater extent than add-on placebo in patients with comorbid obesity and major depression. We will randomize 160 obese MDD patients at 8 recruiting centers to either Simvastatin or placebo as add-on to Escitalopram for 12 weeks. If successful, our trial would have immediate impact on clinical practice given the fact that Simvastatin and Escitalopram are available as inexpensive generic drugs with established safety.

Brief Summary in Scientific Language

Simvastatin is approved for several indications since decades and has in general proven to be an effective and safe medication in primary prevention of cardiovascular disease, which has been linked to both MDD and obesity. Preclinical and clinical data suggest that adjunctive treatment with statins could be useful for the treatment of depressive symptoms. Therefore, in our study, we want to investigate whether add-on Simvastatin to standard antidepressant medication improves depression to a greater extent than adjunct placebo in patients with major depression and comorbid obesity.

Do you plan to share individual participant data with other researchers?

No

Description IPD sharing plan

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Organizational Data

- DRKS-ID: **DRKS00021119**
- Date of Registration in DRKS: **2020/03/17**
- Date of Registration in Partner Registry or other Primary Registry: **2020/03/06**
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **19/0226 – EK 11 , Ethik-Kommission des Landes Berlin**

Secondary IDs

- EudraCT-No.
(for studies acc. to Drug Law): **2018-002947-27**
- Primary Registry-ID: **NCT04301271 (ClinicalTrials.gov)**
- Sponsor-ID: **SIMCODE (Charite University, Berlin, Germany)**

Health condition or Problem studied

- ICD10: **F32.1 - Moderate depressive episode**
- ICD10: **E66 - Obesity**
- ICD10: **F32.2 - Severe depressive episode without psychotic symptoms**
- ICD10: **F32.3 - Severe depressive episode with psychotic symptoms**
- ICD10: **F33.1 - Recurrent depressive disorder, current episode moderate**
- ICD10: **F33.2 - Recurrent depressive disorder, current episode severe without psychotic symptoms**
- ICD10: **F33.3 - Recurrent depressive disorder, current episode severe with psychotic symptoms**
- ICD10: **F34.1 - Dysthymia**

Interventions/Observational Groups

- Arm 1: **Drug: Simvastatin 40mg/day p.o. (tablet), for 12 weeks**
- Arm 2: **Drug: Placebo oral tablet, for 12 weeks**

Characteristics

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Study Type: **Interventional**

- Study Type Non-Interventional: **[---]***
- Allocation: **Randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **patient/subject, caregiver, investigator/therapist, assessor**
- Control: **Placebo**
- Purpose: **Treatment**
- Assignment: **Parallel**
- Phase: **II**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **Yes**

Primary Outcome

- Change score in MADRS (Montgomery-Asberg-Depression Rating Scale); time frame: 12 weeks; The MADRS is a rating scale to measure depression severity. Each MADRS item is rated on a 0 to 6 scale. Total score range from 0-60, where higher MADRS scores indicate higher levels of depressive symptoms.

Secondary Outcome

- MADRS-response (50 % MADRS score reduction from baseline), MADRS-remission (MADRS score < 10), and MADRS-minimal clinically important difference (MCID)
- change Beck Depression Inventory (BDI-II) scores from baseline to week 12, and BDI-II-MCID
- change in Patients' Global Impression of Change Scale (PGIC), change in Clinicians' Global Impression of Severity of illness (CGI-S), Clinicians' Global Impression of Improvement (CGI-I), EuroQol-5 Dimensions-3 Levels Questionnaire (EQ-5D-3L), and Social and Occupational Functioning Assessment Scale (SOFAS) from baseline to week 12

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- **Charité - Universitätsmedizin Berlin, Klinik für Psychiatrie und Psychotherapie, Berlin**
- **Charité - Universitätsmedizin Berlin, Medizinische Klinik mit Schwerpunkt Psychosomatik, Berlin**
- **Universitätsklinikum Frankfurt, Klinik für Psychiatrie, Psychosomatik und Psychotherapie, Frankfurt**
- **Universitätsmedizin Greifswald, Klinik und Poliklinik für Psychiatrie und Psychotherapie, Greifswald**
- **Universitätsklinikum Hamburg-Eppendorf, Klinik und Poliklinik für Psychiatrie und Psychotherapie, Hamburg**
- **Medizinische Hochschule Hannover, Klinik für Psychiatrie, Sozialpsychiatrie und Psychotherapie, Hannover**
- **Universitätsklinikum Leipzig, Klinik und Poliklinik für Psychiatrie und Psychotherapie, Leipzig**
- **Universitätsklinikum Schleswig-Holstein, Zentrum für Integrative Psychiatrie - Klinik für Psychiatrie und Psychotherapie, Lübeck**

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2020/08/13**
- Target Sample Size: **160**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **65 Years**

Additional Inclusion Criteria

- Written informed consent is present
- The patient has the capacity to give consent (He/she is able to understand the nature and anticipated effects/side effects of the proposed medical intervention)
- The patient has a major depressive episode according to DSM 5 (Diagnostic and Statistical Manual of Mental Disorders 5th Edition)
- The patient has a score of ≥ 18 in the Montgomery-Asberg Depression Rating Scale (MADRS)
- The patient has a body mass index ≥ 30
- The patient's age is between 18 and 65 years (≥ 18 und ≤ 65)
- The patient has not given childbirth within the 6 months prior to study entry and is not breastfeeding
- In case of non-psychotropic medication: The patient received stable pharmacological medication for at least 14 days prior to study entry (any changes in medication dose or frequency of therapy must be answered with no)
- The patient did not take antidepressants during the last 7 days prior to study entry (discontinuation of effective medication to enable study participation is prohibited)
- The patient did not receive prior treatment with Escitalopram in index episode
- The patient had less than three (<3) trials with antidepressants in index episode
- The patient does not have a history of non-response to Escitalopram
- The patient did not receive treatment with ketamine, irreversible MAO inhibitor (e.g. tranylcypromine), electroconvulsive therapy (ECT) or other stimulatory treatments in index episode
- The patient does not meet any of the following criteria: schizophrenia, schizoaffective disorder, bipolar disorder
- The patient is not diagnosed with dementia and does not have moderate or severe impairment of general cognitive function according to clinical impression
- The patient does not have clinically relevant elevated liver enzymes [GOT or GPT > 3 x upper limit normal (ULN)] and does not have elevated Carbohydrate Deficient Transferrin (CDT) ≥ 2.4 %
- The patient does not meet the criteria for alcohol use disorder (DSM-5: 303.90; ICD-10: F10.20) or substance use disorder (DSM-5: 304; ICD-10: F11.20 - F19.20) in M.I.N.I. for DSM-5 and a urine/serum drug screening is negative (except for benzodiazepines and opiates)
- The patient does not have a history of suicide attempt
- The patient does not have diagnosed epilepsy or increased bleeding diathesis or a history of angle closure glaucoma or other glaucomas

- The patient did not have bariatric surgery prior to study entry
- The patient does not have a known allergy or contraindication against Escitalopram or Simvastatin
- The patient does not meet any of the following criteria: hereditary muscle disease, known history of rhabdomyolysis, elevated creatine kinase (CK) outside of the sex-specific reference intervals, history of muscular symptoms under treatment with statins or fibrates
- The patient does not have elevated TSH level outside of the age- and sex-specific reference intervals.
- The patient does not have insulin-dependent diabetes mellitus
- The patient does not have uncontrolled hepatic disorder, renal or cardiovascular disease
- The patient does not have untreated hypothyroidism
- The patient does not have a history of myocardial infarction or stroke
- The patient does not have symptomatic peripheral arterial disease
- The patient does not have monogenic familial hypercholesterolemia
- The patient does not have clinically significant laboratory abnormalities
- The patient did not participate in other interventional trials during the 6 months before and at the time of this trial
- The patient is not an employee of the investigator study site, or a family member of the employees or the investigator, or otherwise dependent on the sponsor, the investigator or the investigator study site

Exclusion criteria

- The patient has current use of statins (for visits 2-6 applies: except for IMP Simvastatin)
- The patient has current use of antidepressants (for visits 2-6 applies: except for standard medication Escitalopram)
- The patient has acute suicidal tendencies (MADRS Item 10 > 4)
- The patient uses potent CYP3A4-inhibitors (e.g. clarithromycin, erythromycin, HIV protease inhibitors - see "Risks, adverse drug reactions, drug interactions, restrictions, contraindications, procedures in case of emergency")
- The patient uses potent CYP3A4 inductors (Carbamazepine, Efavirenz, Nevirapine, Etravirine).
- The patient uses Fibrates, Amiodarone, Amlodipine, Verapamil, Fluconazol, Diltiazem, Fusidic acid, Niacin or Lomitapide or BCRP-Inhibitors (e.g. Elbasvir or Grazoprevir)
- The patient uses Gemfibrozil, Ciclosporin or Danazol
- The patient has known hypersensitivity to other ingredients of Simvastatin and Escitalopram [butylated hydroxyanisole, microcrystalline celluose, citric acid, starch, lactose, magnesium stearate, hypromellose, talc, titanium dioxide, iron oxides, colloidal silicon dioxide, croscarmellose sodium, polyethylene glycol]
- The patient uses medication that is associated with QTc-prolongation [antiarrhythmics class IA and III, antipsychotics (e.g. Haloperidol), phenothiazines, tricyclic antidepressants, antibiotics (e.g. Moxifloxacin), and certain antihistaminergic drugs (e.g. Astemizol, Mizolastine)]
- The patient has clinically significant abnormalities in 12-lead ECG (e.g. QTc-prolongation ≥ 500 ms or increase ≥ 60 ms from baseline visit)
- The patient is pregnant
- The patient with childbearing potential is not willing to use an acceptable form of contraception (defined as Pearl index < 1)
- The patient has current use of psychotropic medication (e.g. antipsychotics, anticonvulsants, lithium or St. John's Wort) except for benzodiazepines, non-benzodiazepines and opiates
- The patient uses nonselective, irreversible monoamine oxidase (MAO) inhibitor (e.g. Tranylcypromine) or selective, reversible inhibitor of monoamine oxidase A (e.g. Moclobemide) or the nonselective, reversible monoamine oxidase inhibitor

Linezolid
- The patient is unwilling to consent to saving, processing and propagation of pseudonymized medical data for study reasons
- The patient is legally detained in an official institution

Addresses

■ **Primary Sponsor**

Charite University
Charitéplatz 1
10117 Berlin
Germany

Telephone: **[---]***
Fax: **[---]***
E-mail: **[---]***
URL: **[---]***

■ **Contact for Scientific Queries**

Charite University, Berlin, Germany
Mr. Christian Otte, MD
Hindenburgdamm 30
12203 Berlin
Germany

Telephone: **0049 30 450 617615**
Fax: **[---]***
E-mail: **christian.otte at charite.de**
URL: **[---]***

■ **Contact for Public Queries**

Charite University, Berlin, Germany
Mr. Christian Otte, MD
Hindenburgdamm 30
12203 Berlin
Germany

Telephone: **0049 30 450 617615**
Fax: **[---]***
E-mail: **simcode-studie at charite.de**
URL: **[---]***

- **Collaborator, Other Address**

  NeuroCure Clinical Research Center, Charite, Berlin

  Telephone: **[---]***
  Fax: **[---]***
  E-mail: **[---]***
  URL: **[---]***

- **Collaborator, Other Address**

  University Medical Center Goettingen

  Telephone: **[---]***
  Fax: **[---]***
  E-mail: **[---]***
  URL: **[---]***

Sources of Monetary or Material Support

- **Public funding institutions financed by tax money/Government funding body (German Research Foundation (DFG), Federal Ministry of Education and Research (BMBF), etc.)**

  Bundesministerium für Bildung und Forschung Dienstsitz Berlin
  Friedrichstraße 130 B
  10117 Berlin
  Germany

  Telephone: **[---]***
  Fax: **[---]***
  E-mail: **[---]***
  URL: **www.bmbf.de**

Status

- Recruitment Status: **Recruiting ongoing**
- Reason, if "Recruitment stopped after recruiting started" or "Recruiting withdrawn before recruting started": **[---]***
- Reason, if Reason for Recruiting Stop "Other": **[---]***
- Study Closing (LPLV): **[---]***
- Number of Participants in Germany after Recruiting complete: **[---]***
- Total Number of Participants (all Sites worldwide) after Recruiting complete: **[---]***

Trial Publications, Results and other documents

** This entry means the parameter is not applicable or has not been set.*

**** This entry means that data is not displayed due to insufficient data privacy clearing.*